AMENDMENT

In the Claims:

Please add claim 49 as follows:

49. (New) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent operatively attached to at least a first therapeutic agent, wherein said at least a first targeting agent binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor; and

(a) a targeting agent-detectable agent construct that comprises a second targeting agent operatively attached to a detectable agent, wherein said second targeting agent binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor; or

(b) an anti-cancer agent.

RESPONSE

I. Status of the Claims

Prior to the present Action, claims 1-32 and 43-48 were pending. According to a species election requirement, claims 10-15, 20-23 and 44 are said to be withdrawn as reading on the non-elected species, although these claims have in fact been examined. Presently, no claims have been canceled or amended. Claim 49 has been added, which is unified with the examined claims and is fully supported by the specification.

Claims 1-32 and 43-49 are therefore in the case. In accordance with 37 C.F.R. § 1.121, and for the convenience of the Examiner, a clean copy of the pending claims is attached hereto as **Exhibit A**. As only one new claim has been added, a separate claim exhibit is not necessary.

II. Support for the Claims

Support for the new claim exists throughout the original specification as filed. Any fees necessary for the introduction of the new claim should be deducted from Williams, Morgan & Amerson, P.C. Deposit Account No. 50-0786/3999.002383.

New claim 49 is modeled on claim 1 in this application. The first targeting agent-therapeutic agent construct is even more functionally defined as comprising at least a first targeting agent that binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor. This is supported throughout the original specification, *e.g.*, at page 5, lines 23-24, and at many points thereafter.

The targeting agent-detectable agent construct of optional element (a) is also even more functionally defined as comprising a second targeting agent that binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor, which is supported as described above.

Optional element (b) is simply defined as an anti-cancer agent, which has extensive support throughout the original specification.

It will therefore be understood that no new matter is included in the new claim.

III. Species Issues

Although the Action at page 2, first paragraph, still states that claims 10-5 [*sic*], 20-23 and 44 are withdrawn from "further" consideration, at page 2, second paragraph, it is acknowledged that such claims are entitled to be rejoined in the case upon allowance of a generic claim. As the present response confirms allowability of the generic claims, the claims drawn to originally non-elected species must now be rejoined in the case.

Aside from the procedural issues, Applicants respectfully point out that the claims drawn to the originally non-elected species have already been examined, particularly in the art rejection applied in the second Action. Notably, the elected species of aminophospholipid targeting agent is an antibody or antigen-binding fragment thereof, whereas two of the four references relied upon in the single § 103 rejection at best concern aminophospholipid binding proteins, which correspond to the non-elected species. Accordingly, examination has already focused on the non-elected species, which cannot therefore be characterized as being withdrawn from consideration.

IV. Double Patenting Issues

In reference to co-pending application Serial No. 09/351,457 ("the '457 application"; Attorney Docket No. 3999.002300), which has been allowed, the Action at page 4 states that "prosecution of this application is independent of its co pending counter part". However, Applicants respectfully point out that this is inconsistent with the entry of a double-patenting rejection over claims 1-10 of the '457 application (Action at page 6).

The Action at pages 6-7 states that the subject matter claimed in this application "would be covered" by any patent granted on the '457 application, since the instant application and the '457 application are claiming "common subject matter". The Office cannot take the position that the claims are co-extensive, on the one hand, and that prosecution of the applications is independent, on the other hand.

V. Rejection of All Examined Claims Under 35 U.S.C. § 112, Second Paragraph

The Action first rejects claims 1-9, 16-19, 24-32 43 and 45-48 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite and for failing to particularly point out and

distinctly claim the subject matter of the invention. Although Applicants respectfully traverse, the Action's concerns are fully addressed.

The Action's concerns lie with the recitation of "a second anti-cancer agent" in claim 1, alleging that this is vague, that it is not clear to what agents the Applicants are referring and that the term lacks antecedent basis (Action at page 4).

Applicants respectfully point out that all such issues are addressed in the specification and would be abundantly clear to those of ordinary skill in the art. In particular, the specification states:

> "The 'at least a first anti-cancer agent' in this context means at least a first anti-cancer agent in addition to the therapeutic agent-targeting agent construct of the invention. The 'at least a first anti-cancer agent' may thus be considered to be 'at least a second anti-cancer agent', where the therapeutic agent-targeting agent construct is a first anti-cancer agent. However, this is purely a matter of semantics, and the practical meaning will be clear to those of ordinary skill in the art."
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> Specification at page 39, lines 1-8, emphasis added.

As to the scope of agents to which Applicants refer, the term "anti-cancer agent" is used according to its basic, ordinary meaning: "anti", against; "cancer", malignancy. "Without an express intent to impart a novel meaning to claim terms, an inventor's claim terms take on their ordinary meaning." *York Prods., Inc. vs. Central Tractor Farm and Family Cent.*, 40 USPQ2d 1619, 1622 (Fed. Cir. 1996). Although not believed to be necessary, there is extensive description of anti-cancer agents in the specification, *e.g.*, see Section J of the Detailed Description. Accordingly, the claims are sufficiently definite.

Nonetheless, and without acquiescing with the present rejection in any way, Applicants point out that claim 49 does not include the complained of language.

The rejection under 35 U.S.C. § 112, second paragraph is overcome and should be withdrawn.

VI. Rejection of All Examined Claims Under 35 U.S.C. § 103(a)

The Action next rejects claims 1-9, 16-19, 24-32 43 and 45-48 under 35 U.S.C. § 103(a) as allegedly being legally obvious U.S. Patent No. 6,197,278 to Blankenberg *et al.* ("Blankenberg") in view of Huang *et al.*, *Science*, 275:547-550, 1997 ("Huang"); WO 98/29453 ("the '453 application"); and Fishman *et al.*, *Intl. J. Oncol.*, 10:901-904, 1997 ("Fishman"). Although Applicants respectfully traverse, the Action's concerns are fully addressed.

Applicants first respectfully point out that the references applied in this rejection and the text of the Action at pages 5-6 indicate that all pending claims, including those directed to targeting agents comprising aminophospholipid binding proteins, supposedly drawn to the non-elected species, have already received an examination on the merits (**Section III**).

A. The '453 application is not Available as Prior Art

Before a reference can be used as part of a rejection under 35 U.S.C. § 103(a), it must qualify as prior art under some provision of 35 U.S.C. § 102. As acknowledged by the Action at page 3, this application has an effective priority date of July 13, 1998. The cited '453 application is available as prior art only as of its publication date, which is July 09, 1998, *i.e.*, less than a year before the priority date of the present application. As such, the '453 application is only potentially available under 35 U.S.C. § 102(a) and can be removed as prior art using the mechanism embodied in 37 C.F.R. § 1.131.

Without agreeing with any aspect of the proposed rejection under 35 U.S.C. § 103(a) (**Section VI(b)**), Applicants hereby elect to remove the '453 application as prior art by submitting an inventors' declaration under 37 C.F.R. § 1.131. The enclosed declaration shows

that the present invention was made in the United States prior to July 09, 1998. Although not necessary to antedate the '453 application, from a time prior to July 09, 1998 through July 13, 1998, when the parent of the present application was filed, the inventors worked diligently to reduce to practice additional embodiments of the overall invention.

During preparation of the declaration under 37 C.F.R. § 1.131, evidence of an inadvertent error in inventorship was discovered, which is corrected in the accompanying documents. Accordingly, the enclosed declaration under 37 C.F.R. § 1.131 is properly executed by each of the actual inventors of the claimed subject matter.

The exhibits attached to the declaration present evidence of the facts set forth and meet the requirements of MPEP 715. However, Applicants have elected to proceed under MPEP 715.07 and to remove the particular dates from the exhibits (see section entitled "ESTABLISHMENT OF DATES").

Paragraphs 13 and 14 of the declaration, and Exhibit A, provide evidence of the concept of those aspects of the claimed invention that concern the use of aminophospholipid binding proteins, such as annexins, to target therapeutic agents to tumor blood vessels for tumor therapy, conceived in the United States prior to July 09, 1998. Paragraphs 19 through 24 of the declaration, and Exhibits D through G, provide evidence of the concept of those aspects of the claimed invention that concern the use of anti-aminophospholipid antibodies in targeting therapeutic agents to tumor blood vessels, conceived in the United States prior to July 09, 1998.

Note that Exhibit E of the declaration confirms that the role of Dr. Rote, who supplied certain biological materials for use in the claimed invention, was confined to the provision of such materials to the inventors and does not in any way rise to the level of joint inventorship.

At paragraphs 15 through 18, and in Exhibits B and C, the enclosed declaration provides evidence of the generation and successful *in vivo* use of an aminophospholipid targeting agent-therapeutic agent construct within the scope of the claims prior to July 09, 1998. Exhibit C, in particular, shows the use of a species of aminophospholipid targeting agent-therapeutic agent construct within the claimed invention to successfully treat tumors in controlled studies in animals in the United States prior to July 09, 1998.

It is well established under the law that in order to antedate a reference using a declaration under 37 C.F.R. § 1.131, the declaration is only required to show "as much of the claimed invention as the reference happens to show". *In re Stempel*, 113 USPQ 77 (C.C.P.A. 1957). A reference applied against generic claims may be antedated as to such claims by an affidavit or declaration under 37 C.F.R. § 1.131 showing only a single species of the invention within the claimed genus. *In re Stryker*, 168 USPQ 372 (C.C.P.A. 1971); *In re Spiller*, 162 USPQ 614 (C.C.P.A. 1974). In the present case, Applicants have clearly shown an adequate basis to support possession of the claimed invention prior to the reference date. *In re Wakefield*, 164 USPQ 363 (C.C.P.A. 1970); *In re DeFano*, 157 USPQ 192 (C.C.P.A. 1968); *In re Clark*, 148 USPQ 665 (C.C.P.A. 1966); *In re Schaub*, 190 USPQ 324 (C.C.P.A. 1976).

The enclosed declaration under 37 C.F.R. § 1.131 thus establishes a date of invention in the United States prior to the July 09, 1998 publication date of the cited '453 application, and thus removes the '453 application as prior art.

As the '453 application is not available as prior art, the § 103(a) rejection based upon the combination of the '453 application with Blankenberg, Huang and Fishman is overcome and should be withdrawn.

B. The Proposed Combination Does Not Render the Invention Obvious

Even if the '453 application was available as prior art, the present combination of references fails to constitute a valid rejection under 35 U.S.C. § 103(a). The references have been improperly combined, and even if properly combined, the combination of references would fail to suggest the claimed invention to one of ordinary skill in the art, and even if providing some motivation towards the invention, the combination of references fails to provide the required reasonable expectation of success in achieving the invention.

Blankenberg is first cited as disclosing a method of imaging cell death in cancer cells using radiolabeled annexin (Action at page 5). As Blankenberg does not concern anti-aminophospholipid antibodies, this document has apparently been cited against claims drawn to the non-elected species.

The Action states that Blankenberg does not teach the use of a second anti-cancer agent for therapeutic or diagnostic purposes. Whilst Applicants agree with this deficiency, the Action initially (page 5) appears to have overlooked the fact that Blankenberg fails to teach or suggest the key component of the present invention.

In the kits of the claimed invention, the important element is a targeting agent-therapeutic agent construct comprising a targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent. Thus, the invention claims aminophospholipid-targeted therapeutics, which may be combined with other anti-cancer therapeutics or diagnostics.

Whilst the Action at page 5 contains no mention of therapeutics in connection with Blankenberg, at page 6, the Action characterizes Blankenberg as concerning "imaging or therapeutic methods" and states "because Blankenberg suggests that his methods can be used for

both therapeutic and imaging purposes..." The Action cites no section of Blankenberg in support of such an assessment.

Applicants have studied Blankenberg and believe the document to be limited to diagnostic uses of annexins, and cannot identify any teaching or suggestion of an aminophospholipid-targeting agent therapeutic agent construct. Should the Office maintain the opinion that Blankenberg concerns "therapeutic methods", Applicants most respectfully request that the Office identify the particular section of Blankenberg that is believed to contain the relevant teaching.

As Blankenberg contains no teaching or suggestion of therapeutic constructs targeted to aminophospholipids, it is at best irrelevant to the present invention. To the extent that Blankenberg suggests the use of radiolabeled annexin to image apoptosis (Blankenberg at abstract), this teaches away from the claimed invention, as markers of apoptosis would not be expected to be stable enough to form a viable target. The specification explains:

> "Prior to the present invention, there was mounting evidence that surface PS appears as part of the apoptopic process, marking cells for rapid destruction (Hampton *et al.*, 1996; Martin *et al.*, 1995). Therefore, although reasonable for use as a diagnostic marker for certain disease states, such as graft rejection (Blankenberg *et al.*, 1998), the apparently limited life time of surface PS would also advise against its use as a viable marker for targeting in therapeutic intervention. Nonetheless, the present study did indeed discover aminophospholipids to be markers of tumor vascular endothelial cells suitable for targeting."
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> Specification at page 65, lines 10-18, emphasis added.

In fact, the detailed and groundbreaking studies described in the present application provided the first evidence to show that PS expression on the surface of certain cell types, *i.e.*, tumor vascular endothelial cells, can be separated from the apoptopic process. It is only these types of studies, present in the instant application, but not in the cited art, that allow

aminophospholipids such as PS to be developed as viable targets for the delivery of therapeutic agents. This is also explained in the specification, which states:

> "In fact, the present discoveries have allowed the inventors to show, for the first time, that PS translocation in endothelial cells can occur without significant cell damage or cell death (Example XIV). In the inventors' new model of tumor biology, the translocation of PS to the surface of tumor blood vessel endothelial cells occurs, at least in a significant part, independently of apoptopic or other cell-death mechanisms. Thus, PS surface expression in the tumor environment is not a consequence of cell death, nor does it trigger immediate cell destruction. This is of fundamental importance and represents a breakthrough in the scientific understanding of PS biology, membrane translocation, cell signaling and apoptosis pathways."
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> Specification bridging pages 65-66

The Action is also in error in the characterization of Blankenberg as teaching "targeting radio labeled annexin V directed to a selected organ for any desired condition such as cancer", citing Blankenberg at column 12, lines 33-61 (Action at page 5). Even as pertaining to diagnostics, Blankenberg's connection to cancer concerns "the detection of insufficient apoptosis when it should occur, e.g., tumors or cells infected with virus" (Blankenberg at column 12, lines 36-37).

Blankenberg is further removed from the present invention, and improperly combined with certain of the cited references, as it concerns no reference to tumor vasculature. This is a deficiency in common to the literature concerning the diagnostic uses of annexins prior to the surprising development of the claimed invention (see specification at page 149).

Huang is cited as disclosing methods of occluding tumor vasculature in solid tumors by targeting the cell surface domain of tumor vascular endothelial cells using a bispecific antibody-tissue factor conjugate (Action at page 5). As acknowledged in the Action, Huang does not teach targeting of aminophospholipids. Not only does Huang not "teach" targeting of

aminophospholipids, Huang contains absolutely no suggestion that aminophospholipids could be a targetable component of tumor vasculature.

As the present invention is entirely concerned with aminophospholipid targeting agents and as Huang contains no suggestion of aminophospholipid biology whatsoever, let alone any suggestion that that aminophospholipids could be a targetable component of tumor vasculature, Huang has no relevance the invention. Moreover, Huang has been improperly combined with each of Blankenberg, the '453 application and Fishman.

The Action cites the '453 application[1] as concerning peptide drugs with specific affinity towards phosphatidylserine (Action at page 5). At the time of the second Action, only the English abstract for this Japanese document was available. Applicants have since obtained the English version of this document from the European Patent Office, which has been formally made of record in this case in a Supplemental Information Disclosure Statement.

It will be seen from the enclosed translation that the '453 application does not concern anti-aminophospholipid antibodies as targeting agents. In common with Blakenberg, the '453 application has thus been cited against claims drawn to the non-elected species.

Applicants have endeavored to study the translation of the '453 application, and find the document to be somewhat confusing. Nonetheless, Applicants can find no teaching or suggestion in the '453 application that aminophospholipids are targetable entities of tumor vasculature. Thus, both Blakenberg and the '453 application have been improperly combined with Huang, rendering the § 103(a) rejection improper.

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[1] Applicants respectfully point out that the cited '453 document is only a patent application and not a patent, as quoted in the Action at page 5.

Despite its confusing content, to the extent that the Office still believes the '453 application to be relevant to the presently claimed invention, this document has been removed as prior art by the enclosed declaration under 37 C.F.R. § 1.131, thus removing the '453 application from consideration and destroying the § 103(a) rejection overall.

In common with the '453 application, the Action cites Fishman to "show the general state of art from [*sic*] preparing peptide drugs and autoantibodies directed to aminophospholipids" (Action at page 6).

However, it is well established that simply because a claimed invention is within the level of ordinary skill in the art, this is insufficient to establish a proper case of obviousness. In overturning two obviousness rejections as improperly relying on the high level of skill in the art, the Federal Circuit held:

> "The Board merely invoked the high level of skill in the field of the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness".
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> *In re Rouffet*, 47 USPQ2d 1453, 1456 (Fed. Cir. 1998).

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Dow Chemical Co., supra; In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

The Office has not met any of the foregoing burdens, each of which are required to support a proper § 103(a) rejection. Accordingly, even if each of the four cited documents was available as prior art against the present invention, the § 103(a) rejection fails for at least the foregoing reasons of inadequate teaching or suggestion, improper combination and lack of reasonable expectation of success.

The § 103(a) rejection is thus overcome and should be withdrawn.

VII. Double Patenting Rejection Over the '457 Application

The Action finally provisionally rejects all examined claims under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 in the co-pending, allowed '457 application.

As pointed out above (**Section IV**), Applicants await clarification of the inconsistency in the Action before being able to respond. Should the Office indeed hold that prosecution of these two applications is independent, as stated at page 4, the double patenting rejection must be withdrawn. Should the Office maintain that the proposed double patenting rejection is proper, and that the present claims are not patentably distinct from allowed claims in the '457 application, then the present claims must also be allowable.

Upon confirmation that the present claims are in condition for allowance apart from the double patenting rejection over the '457 application, Applicants will submit a terminal disclaimer to overcome the remaining double patenting rejection, progressing this application to issue.

VIII. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and enclosed documents, the present case is in condition for allowance and such favorable action is respectfully requested. Should Examiner

Sharareh have any questions or comments, or identify any informalities, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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